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EDITORIAL

REGULATING THE SALE OF MEDICINES

CHARLES D. HOWARD, of the New Hampshire Board of Health, preaches from the pulpit of a little periodical called "Health", issued by the department which he so well serves.

For long years he has been the pert exponent of all that is decent and wholesome in the service of public health.

With his pen and his practice he has persistently fought the forces of fraud and corruption in the drug and cosmetic fields.

And he is not just a crusader in words alone, for he deals in deeds as well. The Laboratories of the New Hampshire Board of Health have been his authority and he is girt with their findings whenever he stages a fight.

In the October, 1934, number of his little bulletin he has printed an article dealing with the evils of indiscriminate drug vending and he sees in the spread of this practice a definite danger to public health. For decades, various agencies, such as Dr. Howard's department and the several bureaus of the American Medical Association have conducted campaigns of education designed though not always destined to reach the public. Public school instruction likewise has largely entered into health matters, quackery exposures, etc. State and Federal laws have been applied to curb at least the really rank and dangerous medical frauds, but hosts of these quackeries still persist, and they will continue to exist so long as our laws are as inadequate as they are claimed to be by those best qualified to know.

The tricks of advertising and the tenseness of the times seem to have offset most of the good accomplished by the agencies noted above. Patent medicines are flourishing as they have never flourished before.

And the "indiscriminate vending of drugs" by no means stops with patent medicines. Even the hypnotic and analgesic drugs of

the barbituric class, once considered as strictly prescription materials, are now made as available as air for those who want them.

Department stores and drugless drug stores, and sometimes even the old line pharmacy freely sell these harmful remedies, like any cut price medicine, to all who come to buy them.

The jaded, nervous woman, whose short nights are long and whose long days are short soon finds that "Sleep, the soother of hearts"—can be bought like ribbon at the counter—only that this is as "poppied sleep"—hired, hurt and haunted.

The worried business man, in the red all day, sleeps in the blue with barbital, yet finds that this death of his each day's life sinks his depression still deeper.

The whole thing is wrong!! Valuable drugs these are, when properly administered. In an intelligent physician's hand they are a blessing and boon, but they are much too dangerous for uncontrolled and indiscriminate practice.

According to an article appearing in the Tarrant Co. Medical Society's Bulletin, even the doctor is awakening to the fact that he is used to foster the counter sales of the so-called ethical remedials. We quote from that article:

> "The individual doctor is swamped with free samples. He in turn passes them out indiscriminately to his patients, very often not even removing the label from the bottle. In other cases the name of the product is printed on tins or on a metal cap to a bottle or in some other way so that he cannot remove the name. The doctor thereby becomes the most important factor in advertising the product to the layman. In just this way such items as Petrolagar, Citrocarbonate, Agarol, Viosterol, Halibut Liver Oil, etc., have become extremely popularized so that the layman calls for the item without prescription, and frequently the drug stores and department stores run special sales with these items prominently displayed on counters. The lay purchaser is not in the dark as to their use because full instructions are usually given on the package."

This is, of course, not a novel procedure, for most of our proprietaries got their life-start this way.

There is no doubt that the spread of the drug-less drug store, with its definitely unfair advantage over the old-line pharmacy has made cheaper and tawdrier medicines more available to the public.

But by far the most powerful allies of the quack have been the irresponsible advertising media that have been latterly available to him—and that are for the moment, at least, free of all control.

Hasten the day when the freedom of the press and the freedom of the air as well, in matters such as these, will have become a freedom, well policed and orderly.

IVOR GRIFFITH.

Effects of Tobacco Smoking

The possible important physiologic effects of tobacco smoking have been investigated from several angles. Recently, Dill, Edwards and Forbes (1) reported on the relation of smoking to blood sugar, blood lactic acid and metabolism. The subjects for their experiments remained at rest in the fasting state for ninety minutes before smoking and for forty-five minutes afterward. Each subject smoked one cigarette, inhaling the smoke during a period of from five to ten minutes. Capillary blood was obtained twice before smoking, one or more times during smoking, and frequently during the subsequent forty-five minutes. Three samples of venous blood were also obtained. The sugar determinations were made by the micro method of Folin and Malmros. In addition to observations made on ten subjects in the fasting state, similar experiments were carried out on two subjects beginning about three hours after a light breakfast. They concluded that smoking one cigarette produced no change in blood sugar, lactic acid or respiratory quotient. In regard to oxygen consumption, however, there appeared to be significant alterations subsequent to smoking. While the oxygen consumption after smoking may remain unchanged in some subjects, in others it may increase as much as 10 or 15 per cent. Although this increase is of small magnitude and of doubtful general importance, it does indicate that subjects for basal metabolic rate testing should not smoke in the morning during which the test is to be made.

1. Dill, D. B.; Edwards, H. T., and Forbes, W. H.: Tobacco Smoking in Relation to Blood Sugar, Blood Lactic Acid and Metabolism, *Am. J. Physiol.* *109*:118 (July) 1934.

WHAT ORGANIZED PHARMACY IS DOING ABOUT IT!!

THE Editor of the AMERICAN JOURNAL OF PHARMACY asks a very pertinent question in his November editorial discussing the work of the Committee on Economic Security—"What is organized Pharmacy doing about it?" He points to the fact that a medical advisory committee has come into being because of pressure from the medical profession for participation in the formulation of the principles upon which the proposed social legislation of the New Deal will rest. He infers that the advice of pharmacists has not been asked and probably will not be asked unless organized pharmacy does something about it. He will be glad † to learn that the inference is wrong although by nearly every available precedent his reasoning is entirely correct.

The Committee on Economic Security, made up of the Secretaries of Labor, Treasury, and Agriculture, the Attorney-General and the Federal Emergency Relief Administrator has been busily engaged for some months with a staff of highly competent scientists in the fields of Sociology, Economics and Medicine in drawing up a comprehensive program to give protection to the individual against the vicissitudes and hazards of modern life—unemployment, accident, sickness, invalidity, old age and premature death.

The extent to which advice has been sought from those who may be interested in or affected by a comprehensive program of social insurance has depended upon the sequence in which various phases of the broad problem have been considered and the probable extent of the proposed legislation at the coming session of Congress. It is worthy of note also that the Medical Advisory Committee is composed of individuals representing a variety of points of view. It is not a committee appointed by "organized medicine" with instructions to insist upon a program worked out by one or more associations of physicians. It is exactly what its name implies, an advisory committee picked by the Government from among leading thinkers and doers in American Medicine, regardless of their political or organizational affiliations, but with emphasis upon their record of constructive achievement and broadness of view with respect to the problems to be solved. Neither the Medical Advisory Committee nor those selected or still to be selected to advise on matters relating to dentistry, hospitals, public health or pharmacy, are the result of pressure from

† He is!

anybody or any group. These advisory agencies have been or will be created upon the suggestion of the technical staff of the Committee on Economic Security, which has fully recognized the need for advice and counsel from professional groups.

As early as last October the writer was consulted by the staff of the Committee on Economic Security on the pharmaceutical phases of health insurance. It was pointed out to him that unemployment insurance and old age pensions would in all likelihood be considered first and health insurance would be a later development. However certain pertinent information was desired and it was provided in due course. At the same time assurances were given that if and when any topic affecting pharmacy reaches the point of possible inclusion in a program to be sponsored by the Committee, an advisory committee of pharmacists will be selected and appointed. Such an advisory committee must of necessity include men or women of wide experience who have given some thought and study to the principles of the New Deal and to the systems of medical care in vogue in the United States and foreign lands.

The editor's question therefore takes on a new significance. "What is organized pharmacy going to do about it?" To be asked to give advice and to have a list of names of pharmacists printed on a page of some report is "recognition" of a kind, but what have we to offer in the way of constructive suggestions or a program for fitting the 55,000 or more pharmacies into our changing social structure? Medical and Dental Associations have been at work on the problems of sickness insurance, group practice and other similar developments for some time. They have financed surveys of systems of sickness insurance in foreign countries and have accumulated a body of information that furnishes a basis for advisory work of a high character. What have we done and what have we to offer?

At the meeting of the National Drug Trade Conference, representative of all branches of pharmacy, held in Washington, D. C., December 5, 1934, the following resolution was introduced:

> "The Conference favors a broad spirit of cooperation with the medical and dental professions to the end that matters of mutual professional and economic interest may be considered from the standpoint of the welfare of all of the health professions and the public. In the matter of institutional medical care, group methods of practice, health insurance and various proposals now being advocated to revise the existing methods of providing medical care, the Conference is ready and willing

to supply information and suggestions on all questions with which it is actively concerned, and hereby offers full cooperation to the government and to the medical, dental, nursing and other public health professions."

The resolution could not be passed until the words, "In the matter of institutional medical care, group methods of practice, health insurance and various proposals now being advocated to revise the existing methods of providing medical care," were eliminated, on the ground that the inclusion of these words might be construed as an endorsement of the majority report of the Committee on the Costs of Medical Care.

It must be plain to any serious student of pharmacy that if such foolishness represents "organized pharmacy" it cannot *do* anything about anything. Fortunately, we have within our ranks both the brains and the experience to serve the Government, the profession and the public exceedingly well. It is only necessary to brush aside reactionary influences sufficiently to permit the newly awakened spirit of professional progress to assert itself.

Whether "organized pharmacy" is to be represented now or in the future in national developments affecting the public health and welfare depends entirely upon how rapidly and how well it can develop a viewpoint and a technique that is worthy of professional pharmacy in its finest sense. There never has been and never will be any doubt that *pharmacy* has a place in such developments. The best minds in the Government and in other professions have been most prompt in recognizing that fact.

ROBERT P. FISCHELIS,
President, American Pharmaceutical Association.

ORIGINAL ARTICLES

ROMAN NUMERALS AND THEIR USES IN EARLY MANUSCRIPTS AND BOOKS

By Charles H. LaWall

THE following information is not new, but it will be interesting and perhaps informative, especially to those who have occasion to consult ancient books and manuscripts. We use the so-called Arabic numerals in our daily work in ignorance of or oblivious to, the fact that they really came from India.

In spite of the fact that the great majority of the world's populations could not pass a test in simple arithmetical calculations, including common and decimal fractions, proportion and percentage, the great and decisive progress of the world has been made by mathematicians.

From the time of the ancient Egyptians who oriented their pyramids and temples to the then dominating constellations, through the period of the Babylonians who used astronomy to serve the ends of astrology, (thus making possible a system of fakery which would capture some of the degraded intelligence of the twentieth century) the mathematicians have been the great individuals who have made progress possible in human thought and human development.

Beginning wtih Thales and Pythagoras, progressing through the periods of Democritus, Archimedes, Hipparchus, Heron, Claudius Ptolemaeus, and the other ancient writers on mathematical subjects, down to Roger Bacon, Leonardo da Vinci, Copernicus, Stevin, Galileo, Tycho-Brahe, Kepler, Descartes, Newton, Leibniz, Euler, Gauss, LaPlace, etc., the great minds of the world which have influenced human thought and human progress have been primarily mathematically inclined. The media through which and with which they have worked have been numerals.

Who invented numerals? How have they been evolved?

The average individual pays so little attention to the external form of the figures, and so much attention to their relative position, that he cannot tell, without looking closely, whether Arabic or Roman numerals are used on the dial of the watch or clock which he consults daily, or indeed whether any numerals are employed at all.

It is stated by historians that numbers are older than letters, and if mankind had been furnished with five fingers and a thumb, the world's system of arithmetic would have been duodecimal instead of decimal, which would have necessitated new integers for 10 and 11, and what we now call 10 would have been 12, which would have been divisible by 2, 3, and 4 (instead of only by 2 and 5), and the history of mathematics and perhaps of civilization itself would have been completely changed.

The Egyptians and the Babylonians both employed arbitrary symbols for numerals. The Egyptians had symbols for 1000 (symbolized by a frog) and from that on up to ten millions (the symbol for one of the largest numbers was the figure of a man with his arms outstretched in admiration). The Egyptian system passed through the hieroglyphic to the hieratic form and from that was carried to the Phoenicians and finally to the Syrians. By the time numerals arrived in ancient Greece in the time of Solon (about 600 B. C.) letters came to be substituted for arbitrary symbols.

This system in which letters were used is usually referred to as the Herodian system, after the mathematician of that name who wrote upon the subject about 200 A. D. As used by the Greeks, in this system I stood for one, II for five, Δ for ten, H for one hundred, X for one thousand, and M for ten thousand.

Monogrammatic combinations of these symbols indicated multiples, as II with Δ for fifty, etc. The Hebrews and Syrians influenced this Grecian practice and a new system was evolved in which the first nine letters of the alphabet stood for the units and other letters for multiples of the units.

When the Romans came into the picture, carrying the culture and usages of previous ages we find them adopting symbols from both the Greeks and the Etruscans. The "C", which is customarily believed to be derived from "centum", (one hundred), is really an evolution of the Etruscan sign adapted for this purpose.

The "M" which every schoolboy believes to be the initial letter of the Roman "mille" (a thousand) is really an evolution of the Greek Φ, which, from careless transcribing and false analogy, was later identified with the Greek μ (Mu), and transformed into the letter M.

That this theory is correct is substantiated by the fact that in many of the printed works of the sixteenth and seventeenth centuries the printers tried to set the Greek Φ with available type. The near-

est they could come to it was by using a letter C, making CIↃ for the symbol for 1000, and from this we can easily trace the evolution of the D for five hundred from the IↃ.

The V, which in Roman numerology stands for five is in reality the half of the Etruscan X, which was the symbol for ten, which theory is supported by the fact that there was no letter X in the Roman alphabet. The L, which stands for fifty, was evolved from the half of the symbol for one hundred—C.

While these are more or less speculative views, the fact remains that up to the latter part of the sixteenth century, many printers used the improvised Greek Φ for one thousand, and the separated IↃ for five hundred.

These facts are indispensable for the correct understanding and interpretation of book dates and chapter numerals in printed books prior to the eighteenth century.

When and how the Arabic numerals, which we now employ for all common purposes except dates, came into use, will make a separate story for presentation at some future time.

We do feel sorry, though, for the Roman schoolboys who had to use this cumbersome system (which lacked a decimal point and a zero) in calculating the areas of the public squares or the interest upon the national debt incurred by paying tribute to the Goths.

Happy New Year for CIↃIↃCCCCXXXV!

Cancer Cases Reported From Medicinal Arsenic

Cases of skin cancer caused by arsenic-containing medicines taken for other conditions have caused Drs. Clifford C. Franseen and Grantley W. Taylor of Boston, Mass., to issue a warning to physicians to be very cautious in giving arsenic as medicine.

Nine cases definitely due to arsenic and five more cases probably caused by arsenic are reported by them (*American Journal of Cancer, October*). In two of the cases, the patients had been exposed to arsenic in the form of a spray for fruits and vegetables. But arsenic given as medicine for the relief of skin diseases and blood disorders caused the cancerous condition in the majority of the cases. The arsenic-containing medicine had been taken by some of the patients as long as forty years before the cancerous condition appeared.

Arsenic has been a common constituent of quack cancer pastes, Drs. Franseen and Taylor also pointed out. They hold it has no place in the treatment of cancer.

ALPHA-DINITROPHENOL

ITS PURIFICATION, WITH QUALITATIVE AND QUANTITATIVE DATA

By John C. Bird, Z. Panciera and E. G. E. Shafer

During the course of experimental work in this laboratory upon certain aromatic nitro compounds and their salts, it was found necessary to prepare 2-4 dinitrophenol in as pure a state as possible using simple procedures.

Having regard to the recent interest in the use of this chemical as a metabolic stimulant (J. A. M. A. 101.3.193. 1933), and its possible use in obesity under adequate medical supervision, it occurred to the authors that certain distinctive qualitative tests and quantitative data evolved in connection with this substance might be of some interest particularly to those who might wish to investigate further its medicinal possibilities.

Technical dinitrophenol is available from certain of the larger chemical manufacturing concerns and is thus obtained as a dull brownish crystalline semi-dry paste containing, according to our figures, approximately 8 per cent. of water and possessing a strong characteristic phenolic odor. After several different methods of purification were tried the following was found to give a practically 100 per cent. pure product.

Purification of Crude Dinitrophenol

600 grams of the crude product are stirred with 4000 cc. of water to a homogeneous suspension. To this are added 560 cc. of 20 per cent. caustic soda solution and the whole warmed on the water bath to 70 degrees-80 degrees C. A dark brown solution results to which are added 100 gms. "Norite" carbon. After about five minutes during which the carbon is kept well suspended by stirring the liquid is filtered rapidly whilst still hot, giving a clear amber filtrate. 300 gms. of glacial acetic acid diluted with an equal volume of water and warmed to a similar temperature are now added all at once with vigorous stirring. The liquid clouds slightly but clears almost immediately.

On standing a short time crystallization rapidly sets in and the dinitrophenol is obtained in fine pale yellow leaflets. When the solution is quite cold the crystals are filtered, washed with a little cold water to remove traces of acetic acid, and dried in air. The yield is 505 gms. (about 90 per cent, or 84 per cent. on the crude weight). Hydrochloric acid may be used in place of acetic, but according to

our results the color of the resulting product appears darker although the mother liquid is lighter.

Sodium Dinitrophenate

For the preparation of the sodium salt a similar procedure gives a very desirable product.

1125 gms. of crude dinitrophenol are mixed with 2200 cc. of 10 per cent. caustic soda solution and well stirred to a homogeneous mass. The reaction should be just alkaline to litmus. Water is now added to give a volume of 7500 cc. and the whole is warmed until in solution. The Norite (about 200 gms.) is then added and the liquid after filtering hot is allowed to crystallize. The sodium salt forms bright golden needles. Yield 90 per cent. (or crude weight).

Alpha-dinitrophenol made as described forms pale yellow crystals of m. p. 114 degrees C., very slightly soluble in cold water, more easily on boiling, easily soluble in alcohol, ether chloroform and benzene.

The substance possesses practically no odor and little immediate taste followed later, however, by a slight bitterness.

It should conform to the following qualitative tests:

1. Gently warm a small quantity (.1 gm.) alpha-dinitrophenol in an open crucible over a low flame. The substance melts to a bright yellow liquid and sublimes unchanged.
2. Slowly heat .2 gm. of the substance in an open crucible. The material catches fire and burns quietly evolving carbon. There should be no residue after heating to redness for 15 minutes.

Prepare a .05 per cent. solution of alpha-dinitrophenol in hot distilled water. Allow to cool. The liquid is perfectly clear, transparent and of light greenish yellow color. It is slightly acid to litmus. This solution may be used for the tests.

3. To 5 cc. of above t. s. add 3 drops concentrated H_2SO_4. The solution is immediately decolorized. (Distinction from picric acid).
4. To 5 cc. add 2 drops NaOH solution 20 per cent. The color deepens to golden yellow.
5. To 5 cc. of t. s. add 5 drops of a 10 per cent. solution of KCN. No change in color is noted. (Picric acid gives an amber color, finally turning red).
6. To 5 cc. test solution add 1 cc. of solution of sodium hydrosulphite 1 per cent. to which has been added 2 cc. of 20 per

cent. ammonia solution. Color becomes amber to red, intensified by warming. (Distinction from p-nitro phenol of m. p. 114 degrees C.)

7. To 5 cc. t. s. add 5 drops of saturated sodium sulphide solution. No change takes place. (Further distinction from picric acid, which gives amber red, disappearing on adding a further 5 drops of sulphide.)
8. To 2 cc. t. s. add an equal volume of .04 per cent. Methylene Blue solution. A precipitate of blue black flocks, having a metallic bronze lustre occurs. The precipitate is soluble in excess of water, or on heating, to a bright green solution.
9. To 5 cc. of t. s. add 5 drops 10 per cent. Barium Chloride solution. There should be no precipitate. (Distinction from beta-dinitrophenol.)

The sodium salt is of course more soluble in water than the free dinitrophenol, giving a deep orange to red liquid. The chemical characteristics otherwise are as described for the phenol.

Quantitative Data

For analytical control purposes the water (as water of crystallization) and sodium content were determined as follows:

Weigh accurately 1 to 2 grams of sample in a suitable container (using a platinum crucible or dish if sodium is to be determined on the same sample. Heat in an air oven at 160 degrees to 170 degrees C. for at least two hours, or to constant weight. Cool in desiccator. Weigh. Calculate loss of weight as per cent. total water.

Typical figures are given in the following tables:

No. 1. Weight of Sample—2.3290 grams.

Temperature	Time of heating	Period Loss %	Total loss %
95 to 105°C.	4 hrs.	1.40	1.40
95 to 105°C.	4 "	.36	1.76
95 to 105°C.	4 "	.50	2.26
130°C.	4 "	4.39	6.65
130°C.	3 "	.41	7.06
130°C.	5 "	.78	7.84
150°C.	4 "	.15	7.99
150°C.	2 "	...	7.99
150°C.	2 "	...	7.99
	Total water content		7.99%

No. 2. Weight of sample—1.7894 grams.

Temperature	Time of heating	Total loss %
165°C.	4 hrs.	8.05
170°C.	1 "	8.05
	Total water content	8.05%

From these figures it is evident that it is necessary to heat to 160 degrees-170 degrees C. in order to eliminate all water of crystallization. The literature gives this compound as containing 1 H_2O or 8.04 per cent. with which the above results agree.

Sodium Determination

The following method for the determination of sodium was found to give concordant results. The manipulation is simple, and was devised after several careful attempts at simple ignition had resulted in explosion, and methods of reduction and precipitation had led to more or less complicated procedures.

Method

Weigh 1 to 2 grams of sample in a platinum crucible or dish of at least 25 cc. capacity (the dehydrated material from the total water determination may be used). Moisten the sample thoroughly with about 5 cc. concentrated sulfuric acid, making sure that the entire sample is moistened with the acid. Place in a "chimney heater" and heat in such a way that the entire surface of the crucible is heated gently and uniformly. Gradually raise the temperature until the material is thoroughly charred and there is no more tendency to "creep." Remove the crucible from the "chimney heater" and place directly over a small open flame, being careful to avoid spattering. Finally ignite strongly to a pinkish white residue. Cool. Moisten residue with a few cc. concentrated sulfuric acid. Again evaporate off the acid and ignite. Cool. Weigh as anhydrous sodium sulfate.

$$Na_2SO_4 \times 0.3238 = Na.$$

Calculate per cent. Na on basis of the original sample.

The following table gives figures secured on one sample of the sodium salt of 2-4 dinitrophenol when using this method:

No. 3.

Test No.	Wt. of sample	% Na Found
1	1.3369	10.36
2*	1.7894	10.25
3*	1.0963	10.29
4	1.0982	10.26
	Average	10.29%

*These samples were dehydrated before the sodium determinations were made. Tests 1 and 4 were made on original material.

The average of 10.29 agrees fairly well with the calculated figure of 10.27 allowing for 1 molecule of water and indicates the accuracy of the method. Many trials were necessary however before a satisfactory method of heating could be found owing to persistent creeping of the sample over the sides of the crucible. The "chimney heater" was found to serve the purpose satisfactorily and is merely an indirect heating device. An old ether can (5 lb. size) with the top removed was used in the determinations reported. A nichrome triangle held about midway between top and bottom of the can by running the triangle ends through holes in the sides of the can served as support for the crucible. The purpose of the device is to secure uniform heat on all surfaces of the crucible and its contents. It effectually prevents the beforementioned creeping during the early heating period and eliminates the "spattering" which invariably takes place under direct heat. As with salts of many aromatic nitro compounds our experience with this sodium salt shows it to be much more sensitive to heat than the parent nitro body. The latter may be dried and ignited in a crucible over an open flame using a little care, but it was not found possible to determine ash in the sodium salt in this way.

On heating, sodium dinitrophenate passes through three distinct changes. From the yellow of the crystalline salt, the color becomes increasingly red as the temperature is raised, until the substance fuses to a deep purple or black mass. If the heating is rapid explosion follows immediately after this fusion. If heated slowly the molten material appears to "boil" for some time after which explosion occurs with even greater violence. As small an amount as 0.1 gm. of the salt spread out on an inverted crucible lid will pass through the changes described, finally exploding in what appears to be a vertical plane leaving well marked lines of carbon deposit across the crucible lid. It would appear safe however to heat the salt in an air oven or device as described.—Contribution from the Research Division, John Wyeth & Brother, Philadelphia, Pa.

PREPARATION OF TETRAIODOPHTHALIC ANHYDRIDE

By G. W. Perkins and G. P. Quimba

DURING the course of a study of the X-ray absorption of certain phthaleins, it became necessary to prepare tetroiodophthalic anhydride. The introduction of four halogens into a benzene nucleus obviously would require some powerful halogen carrier or catalyst. Gnehm (1) chlorinated phthalic anhydride in the presence of antimony pentachloride at a temperature of 200 degrees C. to produce tetrachlorphthalic acid. Juvalta (2) catalysed the halogenation with iodine and sulfur trioxide in the form of fuming sulfuric acid. Pratt and Perkins (3) have prepared tetrachlorphthalic anhydride after the method of Duvalta, and Pratt and Young (4) and Pfeiffer and Flater (5) have applied the same principle to the preparation of tetrabromphthalic acid.

Pratt and Shupp (6) prepared tetraiodophthalic anhydride by modifying the method of Juvalta to make it suitable to prepare on a laboratory scale. They do not report any other methods or concentrations of acid as being tried other than 50 per cent. fuming sulfuric acid. We have found in our studies that a large excess of free sulfur trioxide is necessary to catalyze the iodination. Less than 10 per cent. yield of the tetraiodophthalic anhydride with other lower halogenated forms was obtained using 20 per cent. fuming sulfuric acid. With ordinary concentrated sulfuric acid negligible yields of iodophthalic acids were obtained although as long a time as nine hours heating was used in some runs. However, we did note that if a small amount of red phosphorus was added to ordinary concentrated sulfuric acid the effect of the phosphorus was to catalyze the iodination to about the same extent as 20 per cent. fuming sulfuric acid.

Pratt and Perkins (7) found that one equivalent of phthalic anhydride and two equivalents of iodine when mixed with 50 per cent. fuming sulfuric acid and heated at a low temperature (75 de-

(Contribution from the Organic Chemistry Laboratory of the Philadelphia College of Pharmacy and Science and the Emery Laboratory of Cancer Research.)

grees C.) for as long as six days or when heated at a higher temperature (up to 200 degrees C.) for a short period, gave only traces of tetraiodophthalic anhydride while mixtures of di- and tri-iodo-acids or anhydrides were obtained (60 per cent. yield of purified products). They also noted in iodinating the dichlorphthalic anhydrides that when the 3, 6-dichlorphthalic anhydride was iodinated at a comparatively low temperature that tetraiodophthalic anhydride would be formed.

The general method for making the halogen substituted phthalic anhydrides by the method of Duvalta is to dissolve the phthalic anhydride in 50 per cent. fuming sulfuric acid, maintaining the acid at a moderate temperature while introducing the required amount of halogen, then continuing the heating for several hours depending on the halogen derivative being prepared, followed by cooling, pouring on cracked ice, and purification. Pratt and Perkins also found in preparing the di-iodo derivatives that the ratio of the yield of 3, 4 and 3, 6 varieties was changed with change of temperature of the halogenation and that there was no change in the amount of the 4, 5 isomer formed, but that there was a slight increase in tri-iodophthalic anhydride with the higher temperatures. Pratt et al., do not report yields obtained in preparing the tetrachlorphthalic anhydride and report yields of 68 per cent. of the di-iodophthalic anhydrides. They state that they always obtained good yields of tetraiodophthalic anhydride.

We have made a number of preparations of tetraiodophthalic anhydride and find that the strength of the acid is important. In our preparations we used 60 per cent. fuming sulfuric acid (60% free SO_3) while Pratt et al., used 50 per cent. fuming sulfuric acid after the method of Duvalta. Pratt does not give any definite time for heating the reaction mixture, but states it must be heated until the cessation of sulfur dioxide. Practically, this is rather difficult to determine and we have found that good yields could be obtained with definite time and temperature ranges. The following tabulation shows the results obtained in a number of preparations we have carried out using different quantities, temperatures, and mode of addition of iodine.

TABLE 1

Run	Phthalic Anhydride	60% fuming H_2SO_4	Iodine	$C_6I_4(CO)_2O$ yield	Per cent. yield
1.	5 Gm.	40 Cc.	20 Gm.	13.9 Gm.	63.1
2.	10 Gm.	80 Cc.	40 Gm.	34.0 Gm.	77.2
3.	15 Gm.	120 Cc.	60 Gm.	45.0 Gm.	68.1
4.	15 Gm.	120 Cc.	60 Gm.	30.0 Gm.	45.4
5.	15 Gm.	120 Cc.	60 Gm.	55.0 Gm.	83.2
6.	20 Gm.	160 Cc.	80 Gm.	59.0 Gm.	67.0
7.	5 Gm.	40 Cc.	20 Gm.	20.0 Gm.	90.8
8.	25 Gm.	100 Cc.	90 Gm.	94.0 Gm.	85.4
9.	25 Gm.	100 Cc.	90 Gm.	97.0 Gm.	88.1
10.	25 Gm.	100 Cc.	90 Gm.	85.0 Gm.	77.2
11.	25 Gm.	100 Cc.	90 Gm.	83.0 Gm.	75.4
12.	25 Gm.	100 Cc.	90 Gm.	86.0 Gm.	78.1
13.	25 Gm.	100 Cc.	90 Gm.	85.0 Gm.	77.2
14.	25 Gm.	100 Cc.	90 Gm.	85.0 Gm.	77.2
15.	25 Gm.	100 Cc.	90 Gm.	85.0 Gm.	77.2

NOTES

1-3. Oil bath heated to 100 degrees C. and iodine added over a period of 30 minutes. Temperature kept at 100 degrees C. for 5 hours, then heated to 175 degrees C. for 30 minutes and allowed to cool.

4-6. Iodine added at bath temperature of 110 degrees C. Final temperature 175 degrees C. for 30 minutes after heating for 5 hours at 110 degrees C.

7. Iodine introduced at bath temperature of 100 degrees C., oil bath temperature then raised to 135 degrees C. for 5 hours, raising the temperature to 175 degrees C. and immediately cooling.

8. Iodine introduced slowly at a bath temperature of 90 degrees C. Temperature slowly raised to 175 degrees C. over a period of 2 hours, and held there for 15 minutes before cooling.

9. Same as 8. Iodine added at a faster rate.

10. Same as 8. Iodine added in two portions, approximately 60 per cent. first and balance after 30 minutes.

11. Temperature of bath 100 degrees C. during addition of iodine and held there for 3 hours after all iodine was added, then held at 175 degrees C. for 15 minutes.

12-15. Temperature of oil bath held at 70 degrees C. during the addition of iodine and for 2 hours after, then raised to 175 degrees C. and held there for 15 minutes.

The following procedure was then devised based on the findings in the previous table and on other miscellaneous observations. The procedure is somewhat similar to that of Pratt and Shupp (loc. cit.) except for the strength of the acid and the definitely prescribed time for each operation. The *average* yield of the seven runs tabulated below the procedure is 85 per cent. based on the phthalic anhydride. For an oil bath we have found that a ten-quart shallow form ice cream can, set on a single burner gas hot-plate was very satisfactory. This will accommodate several preparations at one

time. The product obtained in these preparations was considered pure enough for the preparation of phthaleins.

Tetraiodophthalic Anhydride.—25 gm. of phthalic anhydride are placed in an 800 cc. Kjedahl flask, followed by 100 cc. of 60 per cent. free SO_3 fuming sulfuric acid. The flask is suspended in an oil bath heated 95 to 105 degrees C., and 90 gm. of finely ground iodine crystals are added to the flask in 2-5 gram portions giving the flask a swirling motion after the addition of each portion of iodine. (A test-tube filled with water may be suspended in the neck of the flask by means of asbestos paper to condense sublimed iodine.) This operation takes about 30 minutes, after which heating is continued at the same temperature for 2 hours more. Finally over a period of thirty minutes the temperature is raised to 175 degrees C. and held there for 15 minutes, and the flask is raised out of the oil bath and allowed to cool to room temperature. The contents of the flask after cooling is then poured into a 2 liter beaker half full of cracked ice. After stirring vigorously and the ice has partially melted, 500 cc. of water are added and sulfur dioxide bubbled through the liquid until most of the iodine is dissolved. The supernatant liquid is decanted off and a liter of warm water added. More sulfur dioxide is passed through the supernatant liquid until it is colorless. A yellow crystalline precipitate settles out. Part of the supernatant liquid is decanted off and the precipitate filtered on a Büchner funnel. The precipitate is washed on the filter with warm water until the washings are free from acid.

The results of several runs made according to the method outlined above is given in Table 2. In runs 2-4 the quantities were varied from those in the rest of the table. In only one run out of a total of twenty-six reported in this paper were we able to obtain a theoretical yield. Pratt on one occasion reports a theoretical yield was obtained and later says that "average yields were obtained."

TABLE 2

Run	Phthalic Anhydride	60% fuming H_2SO_4	Iodine	$C_6I_4(CO)_2O$ yield	Per cent. yield
16.	25 Gm.	100 Cc.	90 Gm.	90.0 Gm.	81.7
17.	20 Gm.	80 Cc.	72 Gm.	79.0 Gm.	91.7
18.	25 Gm.	100 Cc.	90 Gm.	110.0 Gm.	99.9
19.	40 Gm.	160 Cc.	144 Gm.	144.0 Gm.	81.7
20.	25 Gm.	100 Cc.	90 Gm.	95.0 Gm.	86.3
21.	25 Gm.	100 Cc.	90 Gm.	87.0 Gm.	79.0
22.	25 Gm.	100 Cc.	90 Gm.	95.0 Gm.	86.3
23.	25 Gm.	100 Cc.	90 Gm.	88.0 Gm.	80.0
24.	25 Gm.	100 Cc.	90 Gm.	93.0 Gm.	84.3
25.	25 Gm.	100 Cc.	90 Gm.	95.0 Gm.	86.3
26.	25 Gm.	100 Cc.	90 Gm.	91.0 Gm.	82.7

Control analyses were made on all batches of crude product after drying. A persistent impurity not always removed by the sulfur dioxide was free iodine. Sometimes a sample would have a bright yellow color but on control analysis, would have a high percentage of iodine. These samples on heating in an oven at 120 degrees C. over night would lose the adsorbed iodine by sublimation. Pratt and Shupp purified their product further by forming an alkali salt; reprecipitating with acid; heating to form the anhydride, and recrystallizing from nitrobenzene or phenol. The melting point of their product after purification is given as 320-325 degrees C. (cor). Four samples taken from different batches of our crude products melted 323-326; 325-328; 325-327; 325-328 degrees C. Pratt and his co-workers used the lime combustion method for determining the halogen in most of their derivatives. For our control analyses we have used a fusion method using sodium carbonate and sodium peroxide in a nickel crucible. This method was sufficiently accurate for use as a control on the efficiency of our halogenations. We have also used the method of Stepanov and the Thompson-Oakdale method for the iodine content, which in these cases did not seem to be as satisfactory as the fusion method employed.

Method of Analysis: Weigh 0.2000 to 0.3000 gm. of sample and mix with 1.0 gm. of sodium peroxide and 2 grams of sodium carbonate. Both chemicals are reagent grade. Before placing the mixture in a nickle crucible, weigh about 4 gm. of sodium carbonate and pack in the bottom of a nickel crucible (20 cc. size) so that there will be a depression in the sodium carbonate to receive the prepared sample mixture. The prepared sample mixture is then placed in the crucible in the prepared depression. The rest of the crucible is then packed with 13 to 14 gm. of sodium carbonate, which is firmly packed with a glass rod. The crucible is heated over a low flame for 30 minutes after which the flame is encreased and the crucible heated at a cherry red heat for 2 hours. The crucible is allowed to cool to room temperature and carefully dissolved in 450 to 500 cc. of distilled water. Occasionally there is a black residue which is insoluble in the water and is filtered off and the filter thoroughly washed. The washings are added to the filtrate and the whole treated with sulfur dioxide until the solution smells strongly of the sulfur dioxide, 10 per cent. sulfuric acid is then added slowly with constant stirring until acid to litmus. The solution is then heated to boiling and 5 per cent. silver nitrate solution added to precipitate the iodide. Some cloudiness may be present due to sulfur dioxide, this may be cleared up by add-

ing a few cc. of concentrated nitric acid and warming. The solution is digested over a low flame until the silver iodide becomes granular, then filtered through a tared Gooch crucible. The precipitate is thoroughly washed, dried and weighed.

The method of fusion as given above is modified from that of Pitzer (8) who lined the nickel crucible with molten sodium carbonate before adding the sample and peroxide. When the fusion is started at a low heat the loss of iodine through vaporization is negligible, so that for rapid control work it was not considered essential to employ an inverted crucible as in the Piria-Shiff method. Further the limestone used in the latter method is sometimes difficult to dissolve after fusion.

The following analyses represent results obtained on different batches of crude product.

TABLE 3

	Grams Sample	Weight of AgI	Per cent. Iodine
1.	0.2000 Gm.	0.2792 Gm.	75.3
	0.2000 Gm.	0.2810 Gm.	75.87
2.	0.2000 Gm.	0.2886 Gm.	77.91
	0.2000 Gm.	0.2878 Gm.	77.7
3.	0.4133 Gm.	0.5976 Gm.	78.07
	0.4786 Gm.	0.6885 Gm.	77.6
4.	0.2000 Gm.	0.2956 Gm.	79.81
	0.2000 Gm.	0.2952 Gm.	79.20
5.	0.1000 Gm.	0.1478 Gm.	79.81
	0.2000 Gm.	0.2952 Gm.	79.20
6.	0.2000 Gm.	0.2866 Gm.	77.38
	0.2000 Gm.	0.2892 Gm.	78.08

There is a possibility of loss of iodine at two steps in the above analysis, first, in the fusion of the sample, second, during the neutralization of the sodium carbonate. When the sulfuric acid is added too rapidly some iodine vapors will volatilize even though sulfur dioxide is present. The Thompson-Oakdale method gave uniformly low results with these halogen compounds and it was difficult to drive all of the iodine over into the absorption flask, we believe the introduction of an air stream into the reaction flask would help this deficiency. In a later paper we will compare the fusion method above, with the Carius method which is more accurate, but much more tedious and time consuming.

Summary

1. An improved method for the preparation of tetraiodophthalic anhydride has been outlined with which average yields of 85 per cent. may be obtained.

2. The use of 60 per cent. free sulfur trioxide fuming sulfuric acid is essential to the production of good yields of the tetraiodophthalic anhydride.

3. A method of analysis suitable for rapid control work on tetraiodophthalic anhydride has been outlined.

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REPRINTED ARTICLE

THE PREPARATION OF STERILE SOLUTIONS*

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WITH the introduction of the British Pharmacopœia, 1932, official methods of sterilization underwent considerable modification, and the pharmacist was made aware of the inadequacy of the methods which were previously in constant practice. The mere boiling of a solution or steaming at atmospheric pressure were laid aside, and autoclaving, Tyndallization and filtration received official recognition. Results derived from the heat treatment of resistant spores in broths and water apparently justified this conclusion, but there appeared to be little evidence on the effect on micro-organisms of the solutions themselves. With this object in view experiments were commenced; solutions of common hypodermic medicaments were prepared, infected with various types of bacteria, subjected to different methods of sterilization and bacteriologically examined. The results were of such an interesting nature that early publication of the preliminary results seemed advisable in the hope that it might stimulate persons interested in the subject to test and possibly to confirm these results. The writer hopes to continue this subject in a series of papers recording a survey of sterilization as applied to pharmaceutical products.

A synopsis of the sterilization methods of different national pharmacopœias is evidence of the divergence of opinion in regard to the means to be adopted for the production of sterile solutions:

The British Pharmacopœia, 1932:—Autoclaving at 115 degrees to 116 degrees C. (10 lb.) for thirty minutes, Tyndallization in final containers at 80 degrees C. for one hour on three successive days, filtration followed by sterility tests, and an emergency method.

The United States Pharmacopœia, X, 1926:—Autoclaving at 115 degrees C. for thirty minutes, fractional sterilization on three consecutive days in boiling water for fifteen minutes or streaming steam for thirty minutes, and sterilization by filtration.

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The Belgian Pharmacopœia, IV, 1930:—Autoclaving at 120 degrees C., boiling for fifteen minutes, Tyndallization, filtration and preparation with aseptic precautions.

The Swiss Pharmacopœia, V, 1933:—Boiling for twenty minutes, boiling with water for twenty to thirty minutes, heating in free-flowing steam for thirty minutes, autoclaving at 110 degrees to 120 degrees C. for fifteen to twenty minutes, Tyndallization at 60 degrees to 65 degrees C. for one hour on three successive days.

The Italian Pharmacopœia, V, 1927:—Streaming steam for one hour, autoclaving at 112 degrees, 120 degrees and 135 degrees C. for thirty minutes, boiling with water for ninety minutes, Tyndallization at 50 degrees to 60 degrees C. for one hour on five or six successive days.

The German Pharmacopœia, VI, 1926:—Autoclaving at 115 degrees C. for fifteen minutes, boiling with water for thirty minutes, steam sterilizing at atmospheric pressure for thirty minutes, Tyndallization at 70 degrees to 80 degrees C. for forty to sixty minutes on at least four consecutive days the solutions being maintained at about 30 degrees C. in the intervals, and filtration.

The Danish Pharmacopœia, VIII, 1933:—Autoclaving at 120 degrees C. for twenty minutes, streaming steam for one hour, heating at 80 degrees C. for two hours and filtration. The products obtained by methods other than autoclaving, before being decribed as sterile, must undergo sterility tests.

The Dutch Pharmacopœia, V, 1926:—Streaming steam for one hour at 100 degrees C., autoclaving at 107 degrees to 110 degrees C. for thirty minutes, with aqueous liquids by boiling for thirty minutes, Tyndallization at 60 degrees to 65 degrees C. on five consecutive days or at 70 degrees to 80 degrees C. on three consecutive days, and preparation with aseptic precautions.

A lack of unanimity in sterilization methods prescribed by these different authorities is therefore evident.* Autoclaving and Tyndallization are accepted by most as efficient procedures, but there is considerable variation in the other methods. As there appeared to be no doubt of the efficacy of autoclaving and as the result of in-

*While this paper was passing through the press Dr. Hampshire kindly supplied me with the following details from the new *Hungarian Pharmacopœia,* IV, 1934:—Steaming at 100 degrees C. for half an hour, Tyndallization at 70 degrees to 80 degrees C. for forty to sixty minutes on three successive days, the temperature being maintained at 25 degrees to 30 degrees C. between the periods of heating. Details of times and temperatures are varied in special instances.

numerable tests applied to autoclaved products, no further bacteriological investigation of this problem was attempted. Boiling and steaming were then considered. The chief disadvantages in regard to boiling are the necessity to adjust to volume after heating and the enforced use of heat-resisting vessels during the process. Exposure to streaming steam obviates both and an investigation of this process appeared to suggest the most promise.

It is a well-known fact that in the preparation of culture media a single steaming can never be completely relied upon. However, there appeared to be little information in regard to the bacteriological examination of hypodermic solutions submitted to this process. It is obvious from the varied nature of the substances that conditions obtaining in these solutions must greatly differ from those in broths and other culture media. The *p*H of the solution, concentration and osmotic effects and possible bactericidal properties of the solute must of necessity exert some influence on any organisms present. "The rate of disinfection by hot water is greatly increased if the solution is made either acid or alkaline" (Chick, 1910) (1). With this in view experiments were commenced. Determinations of the *p*H of a number of injections were made colorimetrically and, as was to be expected, a great divergence between the acid and alkaline limits was found. The following table shows some of the results obtained.

TABLE I

*p*H	Solutions
7 to 9	25 per cent. caffeine-sodium benzoate (*p*H 8.0), 20 per cent. hexamine (8.2).
6 to 7	0.12 per cent. atropine sulphate (6.8), normal saline (7.0), 5 and 30 per cent. dextrose (7.0 and 6.6), 0.6 per cent. homatropine hydrobromide (6.4).
5 to 6	2 per cent. procaine hydrochloride (5.8), 0.75 per cent. strychnine hydrochloride (5.5), 2.5 per cent. morphine tartrate (6.0).
4 to 5	5 per cent. codeine phosphate (4.7), 3 per cent. pilocarpine nitrate (4.7), 5 per cent. amylocaine hydrochloride (4.9), 2.5 per cent. morphine hydrochloride (4.8), 30 per cent. sodium salicylate (4.4).

A short series of experiments was then made with three of these. The containers used were 25 mil vaccine bottles of neutral glass (Jena). These were sterilized by dry heat and the solutions made with sterile water and infected with suspensions of *Staphylococcus aureus* (twenty-four hour culture) and of *Bacillus mycoides* and *Bacillus subtilis*. These were steamed for five, ten and fifteen

minutes and bacteriologically tested. The staphylococci were killed in five minutes and owing to the ease with which this occurred all future experiments were made with sporing organisms. The results with the other two are formulated in Tables II and III.

One can see the influence of the *p*H of the codeine phosphate solution on the heat disinfection of *B. mycoides*. Owing to the inadequacy of these short exposures to steam the experiments were repeated, the times being fifteen, thirty and sixty minutes, allowing

TABLE II

Solution	Organism	Steaming 5 mins.	10 mins.	15 mins.
0.12 per cent.	*B. mycoides*	+	+	+
Atropine sulphate	*B. subtilis*	+	+	+
5 per cent. Codeine	*B. mycoides*	—	—	—
phosphate	*B. subtilis*	+	+	+
Normal saline solution	*B. mycoides*	+	+	+
" " "	*B. subtilis*	+	+	+

an additional ten minutes for the contents to attain the temperature of the steam.

TABLE III

Solution	Organism	Steaming 15 mins.	30 mins.	60 mins.
0.12 per cent.	*B. subtilis*	+	—	—
Atropine sulphate	*B. mycoides*	+	—	—
5 per cent. Codeine	*B. subtilis*	+	—	—
phosphate	*B. mycoides*	—	—	—
25 per cent. Caffeine	*B. subtilis*	+	—	—
and sodium benzoate	*B. mycoides*	—		—
Normal saline solutions	*B. subtilis*	+	—	—
	B. mycoides	+	—	—

In every case sterile products were obtained after thirty and sixty minutes' steaming. The inhibitory effect of the solution on the growth of the organism in the broth is discounted by the growth which occurred in the test broths for these solutions steamed for only fifteen minutes. Approximately 30 mils of broth were used for 1 mil of the solution and where precipitation of the medium occurred a test using an agar plate was also done in addition to subinoculation of the precipitated broth. All the tests were examined on each day for a total of seven days. Throughout the whole series of tests in this paper if no growth occurred within three days no growth appeared during the remaining four. The tests were carried out in accordance with the directions of the British Pharmacopœia.

Another series of injections was prepared as before and dust, collected from a storeroom in which glassware is unpacked from straw packing material, etc., was used as a further contamination. Examination of the dust-infected material was made only after sixty minutes' steaming.

TABLE IV

Solution	Organism	Steaming 15 mins.	30 mins.	60 mins.
30 per cent. Dextrose	*B. subtilis*	+	—	—
	B. mycoides	+	—	—
	Dust			
5 per cent. Stovaine	*B. subtilis*	—	—	—
	B. mycoides	—	—	—
	Dust			
10 per cent. Soluble barbitone	*B. subtilis*	+	—	—
	B. mycoides	—	—	—
	Dust			—
5 per cent. Calcium chloride	*B. subtilis*	+	—	—
	B. mycoides	+	—	—
	Dust			—

The sterilization of hexamine by the application of heat has been the subject of much controversy, Martindale (2) states that no decomposition of a 40 per cent. solution has occurred on heating for twenty minutes at 100 degrees C. Other references are much too numerous to mention and it was decided to include hexamine and morphine tartrate in this series. As previous experiments had shown the cultures of *B. mycoides* to be not very resistant this was omitted.

TABLE V

Solution	Organism	Steaming 15 mins.	30 mins.	60 mins.
20 per cent. Hexamine	*B. subtilis*	+	—	—
	Dust	+	—	—
10 per cent. Soluble penobarbitone	*B. subtilis*	+	—	—
	Dust	+	—	—
2.5 per cent. Morphine hydrochloride	*B. subtilis*	+	—	—
	Dust	—	—	—
2.5 per cent. Morphine tartrate	*B. subtilis*	+	—	—
	Dust	+	—	—

Soluble phenobarbitone was decomposed during the process; white precipitates rapidly formed in the solution steamed for thirty and sixty minutes and in the course of three days appeared in the one heated for fifteen minutes. Obviously solutions of this substance cannot be subjected to steaming for purposes of sterilization.

A culture of *Clostridium sporogenes* was supplied by Mr. H. Berry as a test organism of the resistant sporing anaerobic type, and this was utilized in the next series instead of the dust which was not as stringent a test as previously anticipated.

TABLE VI

Solution	Organism	Steaming 15 mins.	30 mins.	60 mins.
12 per cent. Sodium thiosulphate	*B. subtilis*	+	—	—
	Cl. sporogenes	+	+	—
0.75 per cent. Strychnine hydrochloride	*B. subtilis*	—	—	—
	Cl. sporogenes	—	—	—
5.0 per cent. Peptone	*B. subtilis*	+	—	—
	Cl. sporogenes	+	—	—
30 per cent. Sodium salicylate	*B. subtilis*	+	—	—
	Cl. sporogenes	+	—	—

The interesting feature of these results is the comparative ease with which these organisms were killed in the strychnine solution. This is in agreement with the results of Todd and Sillar (3), and there can be little doubt that strychnine hydrochloride possesses some germicidal power. In the case of sodium thiosulphate solution the anaerobe was not killed with thirty minutes' steaming. It was therefore resolved in the final series of tests to adopt sixty minutes as the period for steaming.

All the previous experiments appeared to support those statements in favor of sterilizing hypodermic solutions by exposure to streaming steam for one hour. The British Pharmaceutical Codex, 1934, suggests heating to 100 degrees C. for one hour for codeine phosphate and presumably this would be done in a steamer. Thirty minutes is prescribed for a number of other drugs. A series of experiments was suggested to confirm the previous results and to compare these with those produced by the official Tyndallization process. Solutions were prepared with distilled water in vessels, scrupulously cleaned but not sterilized. These were transferred to 25 mil vaccine bottles and plugged with non-absorbent cotton wool. The infecting organisms for the steaming process were *B. subtilis, Cl. sporogenes* and a filtrate prepared from farmyard soil containing straw, stable and poultry manure. A little of this soil was triturated with water and filtered through a coarse filter paper. After boiling a little for seventy-five minutes the liquid was not sterile. As a control a little was mixed with broth and steamed for sixty minutes. On incubation copious growth occurred. Plating and growth in

anaerobic tubes showed the presence in the unheated filtrate of coliform and subtilis-type bacteria and gas-producing anaerobes. Contamination of injections with this material was therefore considered to be a stringent test, the conditions being much worse than any which would be experienced by a person engaged in their preparation. The *p*H of the solutions, both before and after steaming, was determined as appreciable changes would probably indicate a certain degree of decomposition. The subject of decomposition must be treated as a different problem and this paper is concerned essentially with the *bacteriological* control of solutions.

TABLE VII

Solution	Steamed for 60 mins. Soil Filtrate		*B. subtilis* & *Cl. sporogenes*		Tyndallized *B. subtilis* & *Cl. sporogenes*		*p*H	
	Aerobic	Anaerobic	Aerobic	Anaerobic	Aerobic	Anaerobic	Before steaming	After steaming
0.12 per cent. Atropine sulphate	—	—	—	—	+	+	6.6	6.4
5 per cent. Codeine phosphate	—	—	—	—	+	+	4.7	4.7
25 per cent. Caffeine sodium benzoate	—	—	—	—	+	+	8.0	8.0
Normal saline solution	—	--	—	—	+	+	7.0	7.0
5 per cent. Dextrose	—	—	—	—	+	+	7.0	6.0
0.6 per cent. Homatropine HBr.	—	—	—	—	+	+	6.4	6.0
2 per cent. Procaine HCl	—	—	—	—	+	+	6.0	4.2
3 per cent. Pilocarpine nitrate	—	—	—	—	+	—	4.7	4.2

The remarkable fact is evidenced that the Tyndallization process of maintaining at 80 degrees C. for one hour on three successive days is useless when applied to spore infected material, whereas steaming for one hour in every case produced a sterile product. In view of the British Pharmacopœia not specifying the application of sterility tests to Tyndallized products it is evident that in order to place any reliance on the method of solutions *should be prepared with aseptic precautions in previously sterilized containers* before submitting them to the stages of successive heatings. In the remaining series a further step was introduced into the Tyndallization process, a duplicate batch being incubated at 37 degrees C. between the periods intervening between the successive heatings. The temperature inside

the oven was checked by inserting a thermometer through the rubber cap of a vaccine bottle containing water, allowing the temperature of this to reach 80 degrees and maintaining at 80 degrees to 85 degrees C. for one hour. A thermometer in the oven itself was no indication of the temperature attained by the solution.

TABLE VIII

Solution	Steaming for 60 mins. Soil filtrate		Steaming for 60 mins. *B. subtilis* & *Cl. sporogenes*		Tyndallized *B. subtilis* & *Cl. sporogenes* Without incubation		Tyndallized *B. subtilis* & *Cl. sporogenes* With incubation		pH	
	Aerobic	Anaerobic	Aerobic	Anaerobic	Aerobic	Anaerobic	Aerobic	Anaerobic	Before steaming	After steaming
20 per cent. Hexamine	—	—	—	—	—	—	—	—	8.2	9.4
5 per cent. Amylocaine HCl.	—	—	—	—	—	—	—	—	4.9	4.2
10 per cent. Medinal	—	—	—	—	+	—	+	—	9.4	9.4
30 per cent. Dextrose	—	—	—	—	+	—	+	—	6.6	4.6
5 per cent. Calcium chloride	—	—	—	—	+	—	+	—	7.2	7.4
12 per cent. Sodium thiosulphate	—	—	—	—	+	—	+	—	7.4	7.4
2.5 per cent. Morphine HCl.	—	—	—	—	+	+	+	+	4.8	4.8
2.5 per cent. Morphine tartrate	—	—	—	—	+	+	+	+	6.0	6.0
5 per cent. Peptone	—	—	—	—	+	+	+	+	6.0	5.8
0.75 per cent. Strychnine HCl.	—	—	—	—	+	+	+	+	5.6	5.6
40 per cent. Phenazone	—	—	—	—	—	+	—	+	6.4	7.0
30 per cent. Sodium salicylate	—	—	—	—	—	+	+	+	4.4	4.4

Because of the negative results of the anaerobic tests on the first six injections in Table VIII a test was made on the broth culture itself. The result showed that the organism had died in this *without* the application of heat, although it was a living culture when introduced into the solutions. Unfortunately it was not possible to repeat these tests with a fresh culture owing to the limited time available for the completion of this paper. They will be repeated and reported in a further communication. In the remainder a fresh culture was used with the results shown. The aerobic tests on the first six demonstrated that only two were sterile, and it is highly probable that when the anaerobic tests are repeated the result will be different

from those previously obtained. The solution of hexamine was sterile after Tyndallization. This supports the views of Pfister (4) that the decomposition products render the solution sterile after a slight degree of heating. That decomposition does occur to some extent on steaming is evidenced by the change in *p*H from 8.2 to 9.4 and the positive result with Nessler's solution on the steamed product. The test on the unheated control gave a negative result. The results in the case of procaine hydrochloride, pilocarpine nitrate, dextrose and amylocaine hydrochloride appear to indicate some decomposition. The change in *p*H of procaine hydrochloride confirms the results previously published by Rae, but the writer is not convinced that the degree of decomposition is sufficient to condemn this method of sterilization. For many years solutions of this salt heated to 100 degrees C. have been used by anaesthetists, and in the writer's personal experience the anaesthetic action of these preparations has never been questioned. In regard to amylocaine hydrochloride there appears to be more justification for condemnation. In this case the activity of solutions heated to 100 degrees C. or above has been queried, but since the application of the official Tyndallization process there has been no criticism. The above statement is the result of more than five years practical experience in the preparation of these injections for hospital use.

During the progress of this paper the writer was called upon to supply 50 mil ampoules of 50 per cent. dextrose solutions. In accordance with official directions these were autoclaved. On removal from the autoclave the solutions were deep yellow in color due to caramelization, and would obviously have been condemned by the surgeons for whose use they were intended. The Tyndallization process in conjunction with aseptic methods of preparation was therefore applied for all concentrated solutions of dextrose. A series of solutions of 5, 10, 15, 20, 25, 30 and 50 per cent. strength was prepared and sterilized in the autoclave. Above a concentration of 10 per cent. the solutions were colored, the intensity increasing with concentration. The color is also influenced by the reaction of the glass, and if this is alkaline the degree of caramelization is considerably increased. It would therefore seem advisable for the British Pharmacopœia to stipulate a limit of 10 per cent. concentration for solutions to be sterilized in the autoclave. Steaming of a 30 per cent. solution for an hour produces no visible coloration and, as

results have shown, the solution has been sterile even when prepared under conditions of gross contamination. The change in reaction is also greater in the autoclaved solution as shown by the following results.

TABLE IX.—*p*H OF DEXTROSE SOLUTIONS

Concentration	*p*H before sterilisation	*p*H after steaming	*p*H after autoclaving
5 per cent.	7.0	6.0	4.6
30 per cent.	6.6	4.6	4.4

Suggestions have been made (5) that sufficient di-sodium hydrogen phosphate should be added to buffer solutions of dextrose to maintain a *p*H of 7.

SUMMARY.

1. Bacteriological experiments have been made on a number of hypodermic injections showing the results obtained when solutions are prepared under normal conditions.

2. It has been shown that, even in the presence of contamination much worse than that obtaining during any dispensing operations, sterile products can readily be obtained by exposure to streaming steam at atmospheric pressure for one hour.

3. The instructions prescribed by the British Pharmacopœia for sterilization by Tyndallization are inadequate and sterility is not assured.

4. When solutions are incubated during the intervals between successive heatings, the nature of most of the common solutes is such that spores do not pass into the vegetative state and are consequently not destroyed when exposed to a temperature of 80 degrees C. and maintained at 80 degrees to 85 degrees C. for one hour on three successive days.

5. The *p*H of a number of common hypodermic solutions has been determined before and after steaming for one hour and indications of decomposition of the solute are evidenced in certain cases.

6. The sterilization of solutions of dextrose has been investigated and results suggest that concentrations in excess of 10 per cent. should not be sterilized by autoclaving at 10 pounds per square inch pressure.

My thanks are due to Professor C. C. Okell, Professor of Bacteriology in the University College Hospital Medical School,

under whose supervision the work has been done; to Dr. C. H. Hampshire for the information concerning the sterilization requirements of other national pharmacopœias; and to Mr. H. Berry, who has provided facilities for checking many of the above results in the dispensing classes under his control.

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SCIENTIFIC AND TECHNICAL ABSTRACTS

Compiled by Arthur Osol, Ph. D.

Ergoclavine, A New Specific Ergot Alkaloid. W. Küssner. *Arch. Pharm. Berl. 272,* 503 (1934). Through *Quart. Journ. Pharm. Pharmacol. 7,* 618 (1934). The author has obtained from ergot a new alkaloid, ergoclavine, crystallizing in long rectangular plates. The anhydrous base, which is very hygroscopic, melts at 177 degrees to 178 degrees C., and has $[a]_D^{20^\circ} = + 124^\circ$ (1 per cent. in chloroform). Though these figures are close to those for sensibamine, ergoclavine is distinguished from the latter by the fact that it may be recrystallized repeatedly from alcohol or acetone without decomposition. Elementary analysis gave results corresponding to the formula $C_{31}H_{39}N_5O_6$, though, as with other ergot alkaloids, the difficulty of obtaining the material completely anhydrous is a possible source of error. Titration corresponded to a molecular weight of 573. All samples of ergot examined were found to contain ergoclavine, the yields being 16 to 20 per cent. of the total alkaloids for Spanish ergot; 20 per cent. for Russian; and 6 per cent. for Hungarian. Ergoclavine has, qualitatively and quantitatively, the same specific physiological action as ergotoxine.

Determination of Arsenic in Organic Compounds. F. Monforte. *Ann. Chim. appl. Roma. 24,* 105 (1934). Through *Quart. Journ. Pharm. Pharmacol. 7,* 619 (1934). The arsenic in sodium cacodylate can be readily determined in the following way. Melt about 2 grams of sodium hydroxide in a silver or nickel crucible and to the liquid, kept at a temperature of about 350 degrees C., add gradually about 0.1 gram of the cacodylate. When the reaction has ceased, cool and dissolve the contents of the crucible in hydrochloric acid. Add an excess of Bettendorff's reagent, or 50 grams of Bougault's reagent, keep on a water-bath for an hour, filter off the precipitate of arsenic and wash thoroughly. Transfer the filter paper to a stoppered flask, add 50 cc. of N/10 iodine solution and 2 grams of sodium bicarbonate, leave for an hour, shaking occasion-

ally, until all the arsenic has dissolved, and titrate the excess of iodine with N/10 arsenious oxide. For sodium metharsinite heat about 0.1 gram in a Kjeldahl flask with 5 cc. of fuming nitric acid and evaporate the acid to dryness; repeat this three or four times, then add 15 or 20 cc. of strong hydrochloric acid, evaporate to dryness to remove the last traces of nitric acid, dissolve the residue in hydrochloric acid and continue as for sodium cacodylate.

Efficiency of Sodium Benzoate as a Preservative. O. Weider. *Norsk. farm. Tidsskr. 42,* 154 (1934). Through *Quart. Journ. Pharm. Pharmacol. 7,* 632 (1934). The inefficiency of sodium benzoate as a preservative in neutral or slightly alkaline solutions has already been recorded. The author found that, with an aqueous extract of althea, 0.8 per cent. of sodium benzoate was insufficient to prevent growth of moulds, while 0.02 per cent. of benzoic acid was quite effective for this purpose. Sodium benzoate in a concentration of 0.03 per cent. with the addition of hydrochloric acid, was found to be effective when the pH was reduced to below 4, the actual value depending on a number of factors such as the nature of the solution, etc. At pH 1.5 the extract kept free from moulds without the addition of any preservative.

Determination of Small Quantities of Formaldehyde in Mixtures. Fred Thompson. *Chemist and Druggist, 121,* 523 (1934). Most of the available methods for the determination of this substance only give satisfactory results when the formaldehyde is free. When the formaldehyde and its polymers are mixed with other materials the usual methods are found to be very unreliable. Accordingly, the following method is proposed. Transfer 20 grams of the sample to an 800 cc. Kjeldahl flask, add 25 cc. of water and 10 cc. of dilute sulphuric acid and some paraffin to prevent foaming. Steam distill rapidly (about 110 drops per minute, keeping the volume in the distilling flask fairly constant), catching the first 300 cc. (or 200 cc. if extreme accuracy is not desired) in a volumetric flask. Into each of two 50 cc. volumetric flasks run, accurately, 9 cc. of 0.1 N silver nitrate. Add 6 drops of concentrated

nitric acid. To one of the flasks add an excess of potassium cyanide solution—a 0.1 N solution is most convenient. Make up to the mark with water, shake and filter. Pipette 25 cc. of the filtrate into a flask, add 5 cc. of ferric alum indicator, and titrate the excess of silver nitrate with standard thiocyanate solution. This determination serves as the control.

Pipette 25 cc. of the distillate into a small beaker, add the same amount of cyanide solution that was added to the control, and stir well. Transfer this solution to the other volumetric flask, make up to the mark with water, shake and filter. Pipette 25 cc. of this filtrate into a flask, add 0.5 cc. of ferric alum indicator and titrate the excess of silver nitrate with the standard thiocyanate solution. The percentage of formaldyehyde is calculated as follows:

If 300 cc. have been distilled,

(cc. KCNS for sample—cc. KCNS for control) x normality of KCNS x 3.6

If 200 cc. have been distilled,

(cc. KCNS for sample—cc. KCNS for control) x normality of KCNS x 2.6.

The method depends upon the fact that formaldehyde forms an addition product with cyanides and that the cyanide consumed in this reaction does not react with silver nitrate.

Micro-Determination of Acetyl. A. J. Bailey and R. J. Robinson. *Mikrochemie. 15,* 233 (1934). After trying various unsatisfactory modifications, the following procedure was found to yield accurate results. A 5 to 10 mgm. sample is weighed into a small porcelain boat and introduced into a 20 cc. Pyrex flask. 5 cc. of N/25 aqueous sodium hydroxide solution are added to the flask, a micro-reflux condenser attached, and the solution boiled gently for 12 to 35 hours. The time required for complete hydrolysis depends largely upon the character of the acetyl linkage. It has been found that the acetyl-N linkage possesses greater stability than the acetyl-O. After hydrolysis is complete, any alkali adhering to the condenser and rubber stopper is washed into the flask and the excess alkali titrated with N/100 hydrochloric acid using phenolphthalein as the indicator. A blank correction, as determined by a control experi-

ment, is necessary. The authors have found this method to be more accurate than the Pregl-Soltys and Kuhn-Roth methods and report excellent results in the analysis of acetanilid, acetylsalicylic acid, acetyltoluidine, phenacetin, allylisopropylacetylcarbamide and acetaniside.

Determination of Acidity in Non-Aqueous Solutions. O. Tomicek and J. Feldman. *Pharm. Journ. 133,* 595 (1934). The determination of acidic substances insoluble in or immiscible with water has hitherto been difficult, because of the uncertain end-points with ordinary indicators, and was impossible with deeply colored solutions. This led to the use of a potentiometric method with hydrogen, quinhydrone, antimony or tellurium electrodes. The tellurium electrode, which has apparently never before been used in determining hydrogen ion concentration, was found to be most satisfactory between the range pH 5.3 to pH 11.5. It proved to be useful in all the instances of non-aqueous acid solutions that were tried. Solutions of benzoic, oxalic, formic and salicylic acids in such solvents as benzene, methyl, ethyl, isopropyl and amyl alcohols, ether, anisole, hexaline, aniline, acetone and turpentine were all used in testing the suitability or limitations of the potentiometric method. The results compared favorably with those obtained using phenolphthalein as indicator. The antimony and tellurium electrodes gave the best results, especially when lithium chloride was added to the N/10 alcoholic potassium hydroxide solution used for titration. Accurate and reproducible results were also obtained with liquid paraffin preparations and with mixed solvents such as are met with in pharmaceutical work. Samples of linseed and poppyseed oils, preferably dissolved in ether, were readily titrated for free acidity and for saponification values. (October Congress of Slav Pharmacists at Belgrade.)

Determination of Iodides and Bromides in Mixtures. R. L. Raigorodskaja and E. S. Binowa. *Pharm. Zentralhalle, 75,* 609 (1934). The authors suggest a method based upon the U. S. S. R. Pharmacopœia determination of iron iodide in syrup of ferrous iodide. Place 0.1 to 0.2 gram of the mixture in a glass-stoppered flask, add

4 grams of ferric chloride, allow to stand 10 minutes and dilute to 100 cc. with water. Then add 10 cc. of phosphoric acid, mix carefully, add 1 gram of potassium iodide and titrate the liberated iodine with N/10 sodium thiosulphate. Each cc. of this reagent is equivalent to 0.01660 gram of potassium iodide.

The sum of the bromide and iodide is determined by the Volhard method and the bromide content is calculated from the difference between the number of cc. of N/10 silver nitrate used in the former and the number of cc. of N/10 sodium thiosulphate required for the iodide. The results are quite accurate and the method is simple and rapid.

Phenobarbitone and Soluble Phenobarbitone. H. Finnemore. *Australasian Journal of Pharmacy, 49,* 735 (1934). From the number of queries regarding the dispensing of the substances mentioned in the above title, it would appear necessary that pharmacists should come to some agreement among themselves, and with the medical profession, as to the procedure to be adopted when phenobarbitone is ordered in, say, one-half grain doses in mixture form. Accordingly, the following paragraphs have been submitted to the revision committee of the A. P. F. so that order may be brought into the present chaos.

Barbitone and Phenobarbitone: An equal weight of soluble barbitone or soluble phenobarbitone is dispensed if the other ingredients of the prescription are soluble and compatible with them.

Soluble Barbitone and Soluble Phenobarbitone: An equal weight of barbitone or phenobarbitone, respectively, is dispensed if the other ingredients of the prescription comprise substances which will precipitate insoluble barbitone or phenobarbitone. Such are acids, acid salts and acid preparations, e. g., acid syrups and acid infusions (gentian), salts of ammonia and alkaloids. The insoluble barbitone or phenobarbitone will be suspended with compound powder of tragacanth, 5 grains to each fluid ounce.

Syrupus Euphorbiae Compositus. H. Finnemore and E. R. Cole. *Australasian Journal of Pharmacy, 49,* 736 (1934). It has been reported that this syrup gave an unsightly precipitate on standing.

There seemed a possibility that this was caused by the incompatibility of the alkaloids with some tannoid material of the euphorbia, and it was found that this drug does contain tannin, as shown by the green color produced by tincture of ferric chloride. These alkaloidal tannates may be kept in solution by adding a small amount of glycerin. The authors have under observation samples of the syrup containing 5, 10 and 15 minims of glycerin to each fluid drachm, respectively, and will suggest the inclusion of glycerin in the formula if the syrups show no evidence of precipitation on standing.

A Stable Form of Ferrous Chloride. F. E. Carter. *Pharm. Journ. 7,* 389 (1934). The author has performed experiments to show that solutions of ferrous chloride, to which 1 per cent. (W/V) of citric acid has been added, will not oxidize, and will remain bright for a long period. If 5 per cent. of citric acid is used, the solution can be evaporated, and a salt obtained which can be redissolved to give a clear stable solution. Further, ferrous chloride can be made into tablets by using 2 parts of citric acid to 25 parts of ferrous chloride, using dextrose as excipient. These tablets readily dissolve, giving a bright solution.

SOLID EXTRACTS

Hippo-glossus hippoglossus, Linnaeus, is neither a college yell nor the rare name of a rarer orchid. It is piscatorial palaver for the common halibut, whose liver now competes with that of the cod, as a source of vitamin richness. Its expressed oil is tremendously rich in vitamins A and D. Especially A. Think of it—one drop of a good halibut liver oil may contain as much vitamin A as a whole pound of creamery butter and much more vitamin D—which leads us to remark that halibut liver oil is a drug *to be cautiously used, and not a common medicine to be indiscriminately used and abused by anyone who wants to give or take it. Even* scientific medicine *knows too little of these novelties to haphazardly prescribe them.*

Some years ago, before the knowledge of vitamins had reached the profession of medicine, a certain proprietary, cod liver oil wine, was alleged to contain in a non-oily and palatable vehicle, some of the *virtues* of the very oil itself. The then high and mighty authorities in the profession ridiculed and charged as asinine any claim that cod liver oil contained anything else than oil. To be sure, they agreed that cod liver oil expressed from sun-kissed and putrefied livers did contain some alkaloid-like cadaverous compounds, and possibly a little iodine. But nothing else!

How little they knew, as subsequent events have proven.

Yet how strangely that proprietary article continued in sale and used, proving perhaps that the test-tube of time is inevitably firmer in findings than the misguided findings of a science, so-called!

And since liver oils seem to be in good odor at this writing, it may be of interest to note a "brand new use" for oil of the cod. It is now recommended for the treatment of burns. Experimenters have shown that cod liver oil treatment of burns does not influence the primary shock of the burn but is remarkably effective in con-

trolling the secondary infection of large areas. A rapid cleansing of the wound follows its application, and epithelization is stimulated to a degree not seen in any other form of treatment. It is superior to the tannic acid method in that it can be used on the face and in such difficult regions as the buttocks, scrotum and anus. The cod liver oil was used as a salve . . . Attention is called to the fact that commercial cod liver oil is sterile. . . . The experimenters were particularly impressed with the remarkable regeneration of epithelium over large surfaces, such as the entire back.

"Contented cows" have well been called "foster-mothers of the human race." During 1929, for instance, the milk consumption in the United States was 58.7 gallons per capita per year or, on an average, nine pints of milk were consumed by each individual in the United States every week. This is in contrast to 17.6 pounds of butter and 4.6 pounds of cheese per capita per year or 5.4 ounces of butter and 1.4 ounces of cheese per individual per week. Add to this the average per capita consumption during 1929 of condensed milk (2.75 pounds per capita per year), evaporated milk (13.83 pounds per capita per year), and ice cream (twenty-four pints per capita per year), the total will still be a fraction of the per capita consumption of milk as a liquid. A quantity of milk approximately equal to that marketed is estimated to be consumed on farms for feeding humans and animals, etc., and this never enters the market.

For comparison, the consumption of fluid milk per capita per day in the following countries is:

England and Wales—approximately one-half pint; France—one-third pint; Denmark and Sweden—one and one-half pints; and Switzerland, one and four-fifths pints.

One of the latest devices for girth control is the much exploited and tricky Hollywood diet. It consists of a soya bean preparation which is to be used as replacement for one of the big meals of the day. Soya bean meal does contain a little nourishment, but if one really aspires to the shortest distance between the uprights of one's

outline, a more effective, and certainly a cheaper way would be to substitute sawdust for the soya bean. Or better still, do as the Romans did of old with an emetic after dinner, removing the casus belli, yet keeping the tryst with taste.

Nearly one-third of the time, money, and effort expended by the Federal Food and Drug Administration is being devoted to protecting the public from the danger of poisons used in sprays to combat insect pests and diseases that attack fruits and vegetables. This is revealed by W. G. Campbell, chief of the administration in his report to Secretary of Agriculture Wallace which covers the fiscal year ending June 30, 1934.

This agency examined more than 6000 samples of fruits and vegetables to detect poisonous chemicals used in sprays. As a result, fifty-eight consignments containing dangerous quantities of poison residues were seized. Several States were active in making tests to insure safety from poisons. The Director anticipates that it will be necessary to continue the careful watch until science can discover control methods which will make it possible to combat insects and diseases with chemicals which are not dangerous to human beings.

"Crystal crazy" is the charge made by a Federal food authority against a large share of our population. The last year or two has witnessed the development of the new type of medicinal humbug in the marketing of almost innumerable brands of so-called mineral crystals which are essentially laxatives or cathartics and owe their physiological properties to the presence of some well-known therapeutic agent, usually sodium sulphate ("horse-salts"). Medicinal claims of the most extravagant character are made for them and they are sold at outrageous prices. The more adroit manufacturers are careful to restrict such claims to radio and other advertising distributed separately from the interstate package. Where this precaution is taken, action under the Food and Drugs Act is impossible because of lack of jurisdiction.

Probably the earliest book published in the English language on the examination of urine is entitled, "The Judycyall of Uryus," printed in 1512. This is possibly a translation of a manuscript written by Henry Dariel, a monk, in 1379.

"The Differences, Causes and Judgment of Urine," was published in 1541 by Fletcher. He remarked that rhubarb, saffron, cinnamon and broth of cherries, make the urine yellow; cassia, blackish; oil of bay and henbane reddish. He enumerates the sixteen colors of urine, and considers his work complete!

It is hardly believable that nearly fifty million pounds of snuff are manufactured annually in this country although snuff devotees are rarely encountered here.

The use of snuff was once so popular that Pope Urban VIII in 1624 issued an edict of excommunication against its use during church services, because snuffing and sneezing interrupted the religious ceremonies. Its use spread to England, Scotland, and Ireland, and in the eighteenth century snuff taking became the fashion, the lords and ladies taking it in pinches and the scullions and cooks in handfuls. Charles IX, Napoleon, Frederick the Great, Queen Charlotte, Marie Antoinette, all the Georges of England, Lord Nelson, Count von Moltke were devotees of the powdered weed. Dryden, Pope, Swift, Sterne, Addison, Goldsmith, Coleridge, Burns, Doctor Johnson, and other literateurs, took snuff. The method of taking snuff, of opening and tapping the snuff box, became a fine art.

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A—Abstract.
M—Medical and Pharmaceutical Note.
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